

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Klaus BOSSLET et al.

Examiner: Elli Peselev

Serial No.: 10/728,098

Group Art Unit: 1623

Filed: December 5, 2003

Title: EFFECTOR CONJUGATES, METHODS FOR THEIR PREPARATION AND
THEIR PHARMACEUTICAL USE

REPLY

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The issues outstanding in the Final Rejection mailed March 16, 2007, are the rejections under 35 U.S.C. 112, first paragraph. Reconsideration of these rejections, in view of the following discussion, is again respectfully requested.

Rejections Under 35 U.S.C. 112, First Paragraph

Claim 33 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. It is argued, on page 2 of the Office Action, that there is no written description of "m is 3 to 5" in the specification. Applicants' specification defines m, in formula I, as "2 to 5", see page 3, line 4. It is thus clear, under applicable law, that this disclosure supports the narrowed range of 3 to 5. For example, the Federal Circuit's predecessor court has stated that a disclosure of 25 to 60 supported a later claimed range of 35 to 60, holding that, in the area of numerical ranges, the disclosure of a broad range clearly teaches that

Applicants invented, and thus described, all the values within the range. See *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Similarly, the Patent Office own Board of Interferences held that a range of 10 to 79%, with preferred ranges of 40 to 79 and 40 to 60, supported a claim of 10 to 25%. The board held that, in light of *In re Wertheim, supra*, "one of ordinary skill in the art, given [Appellants'] disclosure, would consider that use of the 10 to 25% range would be a part of [Appellants'] invention. "See *McLaughlin v. Roberts*, 197 USPQ 831 (POBI 1978). Thus, the present disclosure of 2 to 5 clearly supports the claimed range of 3 to 5, and withdrawal of the rejection is respectfully requested.

Claims 1-10, 12 and 23-33 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants again respectfully submit that this rejection is in error. The present Office Action fails to provide substantive comment on the majority of the discussion provided by Applicants previously.

Applicants maintain their position that the claimed compounds and methods of use are adequately enabled by the original disclosure when taken in view of the knowledge of one of ordinary skill in the art. Applicants maintain that, despite the disclosure in Nicolau (U.S. Patent No. 6,441,186) cited to support the rejection, the PTO has not sufficiently met its burden of refuting the inventors' statements in the application regarding how to make and use the invention. The burden lies first with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims; see, e.g., *In re Marzocchi et al.*, previously cited. In accordance with *Marzocchi*, the terms of the instant claims correspond in scope with the disclosure regarding the use of the compounds in "treating a disease associated with proliferative processes" (i.e., claim 24) and specific embodiments of such diseases (i.e., claim 25). See, e.g., the disclosure at page 6, last full paragraph, of the instant specification. Also, the terms of the instant claims correspond in scope with the disclosure regarding the use of the compounds in "treating a primary tumor and/or metastases that are not operatively accessible" (i.e., claims 26-28). See, e.g., the disclosure at the paragraph bridging pages 6-7 of the instant specification. The Final Rejection again relies upon Nicolau (as discussed further below) but still fails to provide an explanation of why it doubts the truth or accuracy of these and other statements of the inventors supporting the use of the claimed compounds. The reliance on Nicolau fails to provide a sufficient

basis for any such assertion. The objective evidence of record and known to one of ordinary skill in the art, including Nicolau but considered with the other evidence already of record (e.g., U.S. Patent Nos. 6,982,276 and 7,008,936) is, in fact, supportive of the inventors' statements. See, e.g., the paragraph at the top of page 2 of the disclosure pointing out the knowledge in the art of the very high anti-proliferative activity of epothilone compounds, i.e., the class to which the structure of the effector part of the conjugate of formula (I) belongs. Such anti-proliferative activity of the epothilone class of compounds was well known to those of ordinary skill in the art; see, e.g., U.S. Patent Nos. 6,982,276 and 7,008,936, as just a sample of other references in the art.

The evidence in Nicolau alleged to contradict that Applicants' epothilone conjugate compounds would be useful in treating diseases associated with proliferative processes and particularly for treating a primary tumor and/or metastases is not convincing on this point, particularly in view of the other evidence contradicting it. The general teaching of Nicolau considered as a whole is that epothilones and analogs thereof are expected to have high clinical value due to their toxicity against tumor cells. For example, Nicolau states (col. 1, lines 29-31): "Epothilones are reported to be about 2000-5000 times more potent than Taxol with respect to the stabilization of microtubules." Nicolau also states (Abstract) that: "Several of the analogs are demonstrated to have superior cytotoxic activities as compared to epothilone A or epothilone B." Further, Figures 22 and 23 show that all the epothilone analogs tested by Nicolau demonstrated activity in stabilizing microtubules and in inhibiting human cancer cell lines.

The Final Rejection clings still to the remote statement within Example 5 that "the 4,4-ethano-epothilones proved inactive." However, such statement is not supported by any actual data nor is it provided in any context to determine what was intended by "inactive." It also does not indicate to which 4,4-ethano-epothilones Patentees are referring. Generally, activity profiles of related compounds provide a sliding scale of activity and the probability that a compound related to a compound which is highly active would exhibit absolutely no activity is low. Instead, in the absence of any actual data in Nicolau, one of ordinary skill in the art would have interpreted this statement as meaning that certain 4,4-ethano-epothilones did not meet the threshold assigned for assessing activity in that particular assay. One of ordinary skill in the art would have no basis to conclude from this isolated statement that the 4,4-ethano-epothilones would have no anti-tumor activity whatsoever.

This is particularly the case when the other evidence of record – including the additional evidence discussed below – is considered, since Nicolau provides no actual data to support the statement. Despite clinging resolutely to Nicolau as the basis for its reasoning, the PTO fails absolutely to comment on the foregoing discussion. However, this failure to analyze the specific teaching of the reference underscores the implausibility of the argument built thereupon.

Additionally, Applicants have previously submitted further evidence herewith supporting the activity of the epothilone compounds, by a Declaration under 37 C.F.R. §1.132 (submitted in application Ser. No. 09/485,292) directed to epothilone derivative compounds and use thereof. While the declaration was submitted in that application for the purpose of showing the advantage of 10-ethyl or higher alkyl epothilone derivatives over the corresponding 10-methyl epothilones, the data demonstrate that all the epothilone analogs tested exhibited significant levels of activity in a number of assays connected with anti-proliferative activity. The Final Rejection discounts this data, misapprehending the reason for its submission, arguing that none of the compounds tested is within the scope of the claimed compounds. However, the declaration was not offered as evidence of unexpected results. All of the tested compounds contain, at the position corresponding to the 4,4-position according to Nicolau's nomenclature, dimethyl substitution or spirocyclobutyl substitution. This is significant because the 4,4-ethano-epothilones alleged in Nicolau to be "inactive" fall intermediary between these two structures, i.e., the 4,4-ethano group is a spirocyclopropyl group which has the same number of carbons as the dimethyl analog but has the steric hindrance like the spirocyclobutyl analog and is the adjacent homolog thereto. In view of this evidence and the absence of any actual data in Nicolau, one of ordinary skill in the art would find it highly unlikely that Nicolau actually found or meant to imply complete absence of activity for the 4,4-ethano-epothilones. In view of this data in assessing the evidence as a whole, it is again urged that the PTO's burden of proof is not met.

Finally, even if Nicolau's statement were correct that some 4,4-ethano-epothilones are totally inactive, such would not support non-enablement for applicants' claims as a whole. First, Nicolau does not identify which 4, 4-ethano analogs it is referring to and certainly they did not test all of them. Further, the law is clear that the inclusion of a relatively small number of inoperative species within the generic scope of the claim does not render the claim invalid for non-enablement. See,

e.g., Atlas Powder Co. v E.I. DuPont De Nemours & Co., 224 USPQ 409, 414 (Fed. Cir. 1984), stating:

Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude .. possible inoperative substances.'

As held therein, only if the number of inoperative embodiments is significant does the possibility of invalidity arise. Nicolau does not indicate which specific 4,4-ethano analogs would allegedly be inoperative so no support is provided that a large number of them would be inoperative. In any event, this would only be a small portion of the scope of applicants' claims.

For all of the above reasons, it is urged that the PTO has not met its initial burden of proof of non-enablement and, at least for this reason, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Final Rejection also again refers to four of the "Wands" factors in the enablement rejection. As previously noted, the Wands decision pointed to consideration of eight factors. It was previously stated to be assumed to be admitted that the other four factors not addressed in the office actions weigh in favor of enablement. The Final Rejection does not dispute this. It is again emphasized that these factors are all considered together and, thus, one will not alone support lack of enablement. It is clear that a balancing of all of these factors does not support a non-enablement rejection. Applicants have the following comments regarding each factor:

- Breadth of Claims - The scope of the methods treated is no broader than the acknowledged and known activity in the art of epothilones as anti-proliferatives. Applicants' invention recognizes the previous art of epothilone analogs as anti-proliferatives and does not rely on this aspect for novelty. Thus, the breadth of the claims as to encompassing epothilone analogs is not a proper basis upon which to allege non-enablement. The activity and use of epothilone analogs relied on for the invention is known to those of ordinary skill in the art. Instead, the invention is characterized, in part, by the conjugation of the epothilone with a linker-recognition unit. In this respect, the claim is not particularly broad since it specifies the positions of the linking L groups and the structure of the linkages and also the structure of the EG recognition units

attached by the linking groups.

- State of the Prior Art - As admitted in the Office Action, epothilones are known as antiproliferatives and anti-tumor agents. This factor weighs heavily in support of enablement since it would not involve undue experimentation for one of ordinary skill in the art to use applicants' novel conjugate compounds in methods analogous to the known methods. There is no allegation in the Office action that the state of the prior art supports non-enablement.
- Nature of the Invention - As pointed out above, the nature of the invention lies, in part, on the conjugation of the epothilone with a linker-recognition unit and there is no allegation in the Office action that the nature of the invention supports non-enablement.
- Level of Ordinary Skill - The M.D. or Ph.D. skill level, admitted in previous Office actions, is a very high skill level which also weighs in favor of a finding of enablement. There is no allegation in the Office action that the level of ordinary skill supports non-enablement.
- Predictability in the Art - Applicants submit that the level of unpredictability is not particularly high given the admitted state of the prior art regarding epothilone analogs and the ability of one at a high level of skill in the art to analogously apply applicants conjugate compounds to the known uses of epothilones. The allegations of unpredictability based on the Nicolau reference are discussed above and that discussion is incorporated herein by reference. Further, the standard for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).
- Direction Provided by Inventor - As discussed above, the specification points out the known activity of epothilones and the specification exemplifies a number of particular diseases for which an antiproliferative effect is desired. The knowledge of one of ordinary skill in the art as to the antiproliferative effect of epothilone analogs is also applicable here. Further, there is no allegation in the Office action that this factor supports non-enablement.
- Existence of Working Examples - Although there are no working examples of methods

of treatment in the disclosure, the law is clear that it is not necessary to provide working examples in order to enable the invention; see, e.g., In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970); and, In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). The known antiproliferative effect of epothilone analogs makes confirmation of such known fact in this application unnecessary. Although unnecessary, the data provided in 132 Declaration filed herewith, support the activity of a epothilone analogs in assays which support their antiproliferative effect.

- Quantity of Experimentation Needed - Applicants respectfully submit that the quantity of experimentation needed is not excessive because the type of experimentation that one of ordinary skill in the art would need to conduct is only routine experimentation due to the known activity and uses of the epothilone analogs and the high level of skill in the art. That some experimentation is required does not support a finding of non-enablement; lack of enablement only arises when the experimentation required is undue. The Office Action states that there is no way to predict which compounds will be active. It may be true that it cannot be absolutely predicted a priori whether a particular compound will be active, but absolute predictability is not required. As pointed out above, based on the knowledge in the art (and supporting data in the art and in the 132 Declaration) one of ordinary skill (a high level of skill here) in the art could reasonably expect that the epothilone analogs will exhibit an antiproliferative effect and would only need to conduct routine experimentation to determine such.

The above factors clearly balance in favor of the instant claims being enabled to one of ordinary skill in the art. There is no basis to suggest that one of ordinary skill in the art could not use applicants epothilone conjugate compounds in methods substantially analogously to methods in which known epothilone analog compounds are used.

For all of the above reasons, it is once again urged that the specification viewed in light of the knowledge of one of ordinary skill in the art (a high level of skill here) adequately teaches how to make and use the claimed invention. Thus, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The claims are accordingly submitted to be in condition for allowance, and passage to issue is respectfully urged. Should the Examiner have any questions or comments, she is cordially invited to telephone the undersigned at the number below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/Harry B. Shubin/

Harry B. Shubin, Reg. No. 32,004
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: DORRIE-0007

Date: July 12, 2007

HBS/pdr

K:\Dorrie\7\amendment 2 1-26-07.doc